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Synthesis of bicyclic alcohols by palladium-catalyzed Et_2Zn-mediated intramolecular carbonylpropargylation

Mónica Arrate and José M. Aurrecoechea*

Departamento de Química Orgánica II, Facultad de Ciencia y Tecnología, Universidad del País Vasco UPV/EHU, Apartado 644, 48080 Bilbao, Spain
Email: jm.aurrecoechea@ehu.eus

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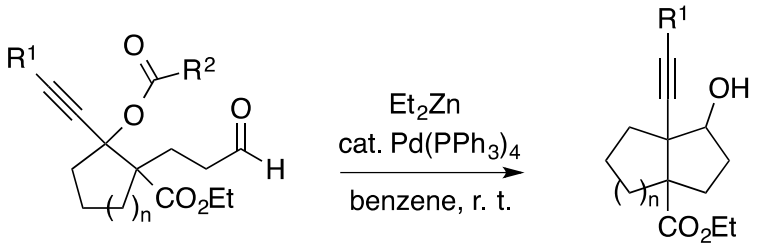
Abstract

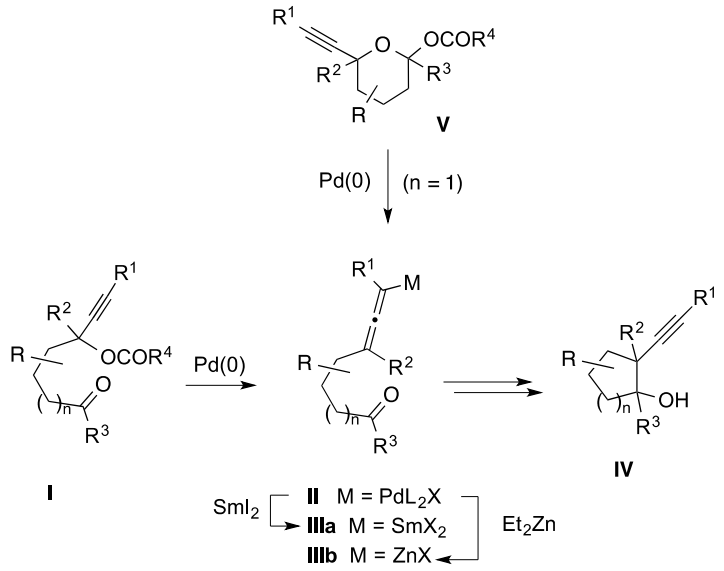
Propargylic esters derived from cyclic ketones containing a tethered aldehyde generate bicyclic homopropargyl alcohols upon treatment with Et_2Zn in the presence of a catalytic amount of Pd(0). The reaction is thought to involve an intramolecular carbonyl addition of intermediate allenylzinc nucleophilic species generated from the propargylic ester functionality. The resulting trisubstituted bicyclic products are obtained with high stereoselectivity. Examples are provided where the reaction is successfully applied to both cyclopentanone- and cyclohexanone-derived substrates containing either terminal or internal alkyne, thus overcoming some of the limitations previously encountered with the use of alternative methodology.



Keywords: Cyclization, palladium, propargylation, allenylpalladium, diethylzinc

Introduction

Propargylic esters are a convenient type of functionalized reagent because they are stable, readily available and easy to handle. Among other applications, propargylic esters are precursors of nucleophilic organometallic species that behave as synthetic equivalents of the propargyl anion, participating in nucleophilic addition reactions to carbonyl or imine derivatives.[1-3] We have exploited this particular reactivity of propargylic esters (and related substrates) in SmI_2-promoted Pd-catalyzed intramolecular propargylations of carbonyl derivatives to generate alkynylcycloalkanol derivatives.[4-8] These reactions are thought to proceed *via* transient allenylpalladium **II** intermediates that undergo transmetalation with SmI_2 to generate nucleophilic allenylsamarium species **IIIa** capable of carbonyl nucleophilic addition (Scheme 1). A variant was also developed where acetal-type derivatives **V** were used as masked aldehydes to generate the same intermediates.[6-8] Particularly interesting was the case of formation of bicyclic alkynylcyclopentanol products, compounds that have attracted attention as synthetic intermediates[9-11] and as components of therapeutically interesting molecules related to prostaglandins.[12-19] A high stereoselectivity was observed in that case,[4,5] but some limitations were also found. Thus, only ketone carbonyls could be used in combination with the propargylic esters **I**,[5] and the reactions of acetals **V** were limited to terminal alkynes. Furthermore, only the [3.3.0] ring fusion was accessible when forming bicyclic products from acetals **V**.[6]

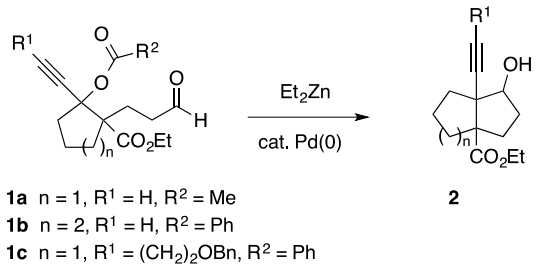


Scheme 1. Pd(0)-Catalyzed synthesis of homopropargyl cycloalkanols.

Alternatively, the use of Et_2Zn as transmetalating agent has also been reported, and in this case the method has been shown to be compatible with the use of aldehydes.[1,2] This variant, proceeding through the corresponding allenylzinc intermediates **IIIb**, has been applied both inter- and intramolecularly, albeit only with linear acyclic substrates in the latter case.[20,21] We now report the application of the Pd(0)/Et_2Zn-promoted intramolecular propargylation of carbonyl compounds to the preparation of bicyclic alkynylcyclopentanols from aldehyde-tethered propargylic ester substrates, whereupon previous limitations of the use of these substrates are overcome.

Results and Discussion

We have used aldehydes **1a-c** as precursors of target bicyclic structures **2**. The selected examples feature cases with both terminal and internal alkynes, as well as two different types of ring fusion.

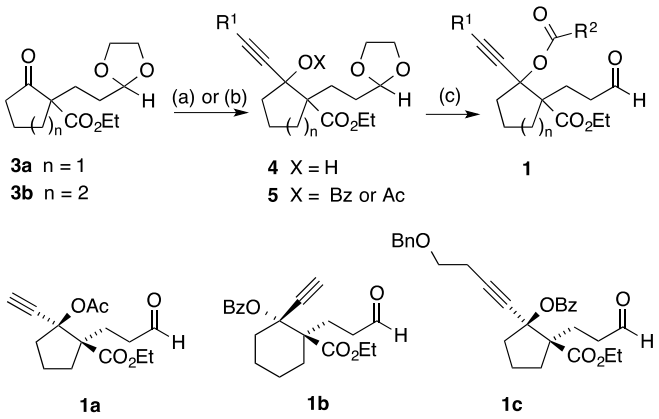


1a n = 1, R^1 = H, R^2 = Me
1b n = 2, R^1 = H, R^2 = Ph
1c n = 1, R^1 = $(CH_2)_2OBn$, R^2 = Ph

2

Scheme 2. Projected synthesis of bicyclic alcohols from cyclic propargylic esters.

Substrates **1** were straightforwardly prepared by alkynylmetal carbonyl addition to monoprotected 1,5-dicarbonyl derivatives **3**, followed by esterification and carbonyl deprotection (Scheme 3).



3a n = 1
3b n = 2

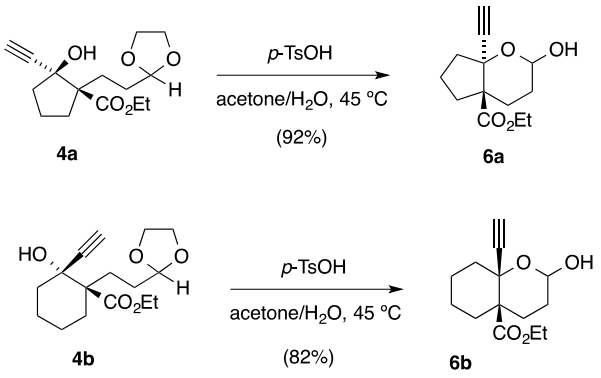
4 X = H
5 X = Bz or Ac

1

1a **1b** **1c**

Scheme 3. Preparation of propargylic esters **1**. Reagents: (a) (*i*) Ethynylmagnesium bromide, THF, -20 °C to rt; (*ii*) H_2O (**4a** and **4b**); (*iii*) Ac_2O, Et_3N, DMAP, rt (**5a**). (b) (*i*) R^1-C≡C-M (M = Li or MgBr), THF, -20 or 78 °C to rt; (*ii*) BzCl, rt (**5b** and **5c**). (c) AcOH/H_2O, reflux.

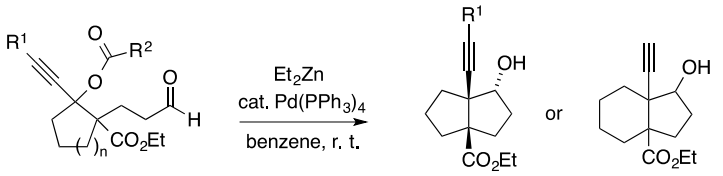
Carbonyl addition took place in ketones **3** with very high diastereoselectivity and, as a result, products **1a-c** were obtained nearly as single diastereoisomers. The stereochemical assignments of **1** were made after conversion of intermediate alcohols **4a** and **4b** into the known lactols **6a** and **6b**,[6] respectively, by hydrolysis of the cyclic acetal unit (Scheme 4). The stereochemistry of **1c** was assigned by analogy with that of **1a**. In any case, the relative configuration of substrates **1** is likely to be of no consequence in their cyclization reactions since the putative intermediates, allenylzincs **IIIb** (Scheme 1), are expected to be of limited configurational stability at r.t.[22,23]



Scheme 4. Conversion of hydroxyacetals **4** into lactols **6**.

Starting from esters **1**, the expected bicyclic products **2** were obtained in moderate to good yields upon treatment with Et_2Zn in benzene, in the presence of a catalytic amount of $Pd(PPh_3)_4$ (Table 1). The alternative use of THF as solvent or P(*n*Bu_3) as ligand[21] led to very low yielding reactions with substantial substrate degradation. Remarkably, under the conditions indicated in Table 1, the cyclization took place with high stereoselectivity, affording usually a single isomer. The yield of bicycles **2b** and **2c** improved when the reaction was run in the presence of $ZnCl_2$ (entries 3 and 5), which presumably acted as a Lewis acid to activate the carbonyl group towards nucleophilic attack. From the methodological point of view, these reactions either complement the previously reported Pd(0)/SmI_2-promoted cyclizations or provide an alternative to those cases where that methodology had failed.[4-6] Thus, the preparation of **2a** had only been possible through acetals of type **V**,[4] and now this product becomes available also from an aldehyde substrate by using Pd(0)/Et_2Zn conditions. On the other hand, for aldehyde-type substrates, products containing an internal alkyne or a [4.3.0] ring fusion (case of **2c** and **2b**, respectively) had not been accessible previously using the Pd(0)/SmI_2 methodology.[6]

Table 1. Preparation of bicyclic 2-alkynylcyclopentanols **2** from propargylic esters **1**[a]



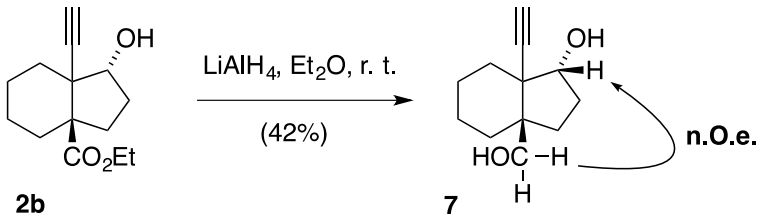
1a-c **2a, 2c** **2b, 2b'**

Entry	n	R^1	R^2	t (h)	**2**	Yield[b]	d. r.
1	1	H	Me	0.5	**2a**	70	≥ 50:1
2	2	H	Ph	1.5	**2b**	39	≥ 50:1
3[c]	2	H	Ph	0.1	**2b**	58	4.3:1
4	1	$(CH_2)_2OBn$	Ph	6	**2c**	43	≥ 50:1
5[c]	1	$(CH_2)_2OBn$	Ph	0.5	**2c**	72	≥ 50:1

[a] Reaction conditions: Unless otherwise indicated, **1** (0.3 mmol), $Pd(PPh_3)_4$ (5 mol%), Et_2Zn (3 equiv) in benzene (3 mL) at room temperature. [b] Isolated yield (%). [c] $ZnCl_2$ (1.2 equiv) was used as additive.

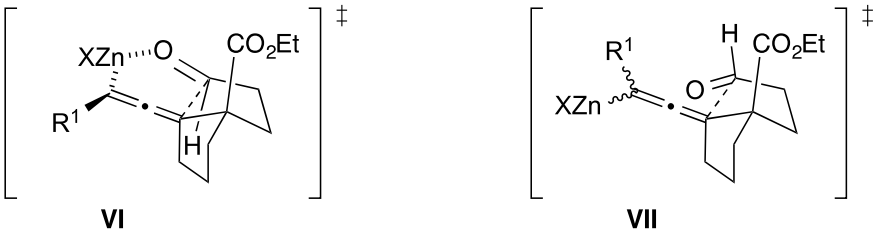
The stereochemical assignments of products **2a** and **2c** were made based on that of **2a**, which had been previously reported.[4] Additionally, products **2a** and **2c** had very similar NMR characteristics, particularly

concerning the critical ^{1}H- and ^{13}C-NMR resonances at the carbinol and ring fusion positions.[24] In the case of the major isomer **2b**, it was established that the OH and CO_2Et groups were *trans* to each other, after LAH reduction of the ethoxycarbonyl group and the observation of n.O.e. between the carbinolic methine and methylene hydrogens of the resulting diol **7** (Scheme 5). However, the relationship between those groups and the alkynyl moiety of **2b** remains ambiguous.



Scheme 5. Reduction of ester **2b** to alcohol **7**.

The preparation of bicyclic products **2** involves a ring-closure that generates a 2-alkynylcyclopentanol moiety where two new stereogenic centers are generated with high stereoselectivity. Simple monocyclic 2-alkynylcyclopentanols have been similarly prepared from the corresponding acyclic propargylic esters.[21] In that case, the *cis*- or *trans*-relationship between the alkynyl and hydroxyl functionalities was shown to depend on the choice of phosphine and solvent, and for simple aldehyde substrates, this particular combination of $Pd(PPh_3)_4$ as catalyst and benzene as solvent had led to low stereoselectivities.[21] It is likely that the high levels of stereocontrol observed in the present cyclizations, particularly in the case of [3.3.0] ring fusion, are due to the rigidity of the newly generated bicyclic system. Thus, a *cis*-ring fusion would be expected to be preferred on thermodynamic grounds.[25] Additionally, a chelate arrangement of type **VI**, analogous to the one typically invoked in the intermolecular reactions of allenylzincs with carbonyl compounds,[26] might be difficult to attain in this case due to its presumably strained tricyclic nature. As a result, the reaction may proceed through an "open" transition state **VII** leading to a *trans* relationship between alkynyl and hydroxyl groups.



Conclusions

The application of the Et_2Zn/Pd(0)-mediated intramolecular propargylation of aldehydes from carbonyl-tethered propargyl esters has been successfully extended to the stereoselective preparation of bicyclic cyclopentanols. This reaction circumvents some limitations previously encountered in the preparation of those compounds with related methodologies. Specifically, aldehydes are directly employed without resorting to masking procedures, both internal and terminal alkynes participate effectively, and the preparation of [3.3.0] as well as [4.3.0] bicyclic systems has been demonstrated.

Experimental Section

General. All reactions involving air- and moisture-sensitive materials were performed under an argon atmosphere using standard benchtop techniques. Tetrahydrofuran (THF) was freshly distilled from sodium/benzophenone. Other solvents were routinely purified using literature procedures. Analytical thin layer chromatography (TLC) was performed on aluminum plates with Merck Kieselgel 60F254 and visualized by UV irradiation (254 nm) or by staining with an ethanolic solution of phosphomolibdic acid. Flash column chromatography was performed on silica gel (230-400 mesh). HPLC purifications were carried out with a LiChrosorb Si60 (7 m, 25 x 2.5 cm) column using a refraction index detector. ^{1}H NMR spectra were obtained at 250 MHz in $CDCl_3$ at ambient temperature, with residual protic solvent as the internal reference (δ_H = 7.26 for $CHCl_3$). ^{13}C NMR spectra were recorded at 62.9 MHz in $CDCl_3$ at ambient temperature, with the central peak of the solvent (δ_C = 77.0 for $CDCl_3$) as the internal reference. The DEPT sequence was routinely used for ^{13}C multiplicity assignment. Infrared spectra (IR) were obtained from a thin film deposited onto a NaCl glass and data include only characteristic absorptions. Mass spectra were obtained at 70 eV.

(1*R,2*S**)-Ethyl 1-[2-(1,3-dioxolan-2-yl)ethyl]-2-ethynyl-2-hydroxycyclopentane-1-carboxylate (4a)**. To a solution of **3a**[27] (1.9 g, 7.6 mmol) in THF (50 mL) at -20 °C under Ar was added ethynylmagnesium bromide (0.5 M in THF, 16.2 mL, 8.1 mmol) dropwise. The solution was allowed to reach room temperature and stirred 1 h. Saturated NH_4Cl (20 mL) was added, the layers were separated, and the aqueous layer was extrated with EtOAc (3 x 40 mL). The combined organic layers were dried (Na_2SO_4), the solvents were evaporated and the crude product was purified by flash chromatography (silica gel, 80:20 hexanes/EtOAc) to yield **4a** as an oil (2.1 g, 97%): ^{1}H NMR δ 1.23 (t, *J* 7.1 Hz, 3H, C*H*$_3$), 1.44-1.77 (m, 6H), 1.90-2.01 (m, 2H), 2.22 (m, 2H), 2.43 (s, 1H, H-2''), 3.07 (s, 1H, O*H*), 3.46-3.94 (m, 4H, OC*H*$_2$C*H*$_2$O), 4.14 (q, *J* 7.1 Hz, 2H, $CO_2CH_2CH_3$), 4.80 (m, 1H, O-C*H*-O). ^{13}C NMR δ 14.1 (CH_3), 17.9 (CH_2), 24.9 (CH_2), 29.1 (CH_2), 29.2 (CH_2), 37.4 (CH_2), 60.4 (C-1), 60.6 (CH_2), 64.7 (CH_2), 72.7 (C-2''), 77.0 (C-2), 85.9 (C-1''), 103.9 (O-*C*H-O), 174.5 (*C*=O). IR (neat) 3600-3400 (br, O-H), 3300-3200 (m, ≡C-H), 3000-2800 (m, C-H), 2100 (w, C≡C), 1730 (s, C=O), 1270 (m, C-O-C) cm^{-1}.

(1*R,6*S**)-Ethyl 6-ethynyl-4-hydroxy-5-oxabicyclo[4.3.0]nonanecarboxylate (6a)**. A solution containing acetal **4a** (0.32 g, 1.15 mmol) and *p*-TsOH (0.115 mmol) in acetone/H_2O (15:1, 40 mL) was stirred at 45 °C until complete disappearance of the starting **4a** (TLC). Sat. $NaHCO_3$ (4 mL) was added and the mixture was evaporated to dryness. The residue was partitioned between H_2O (4 mL) y Et_2O (20 mL). After separation, the aqueous layer was extracted with Et_2O (3 x 6 mL) and the combined organic layers were dried (Na_2SO_4). The residue after evaporation was purified by flash chromatography (silica gel, 80:20 hexanes/EtOAc) to yield lactol **7a** as an oil (0.25 g, 92%): ^{1}H NMR δ 1.26 (t, *J* 7.1 Hz, 3H, C*H*$_3$), 1.44-1.59 (m, 1H), 1.72-2.14 (m, 7H), 2.19-2.45 (m, 2H), 2.49 (s, 1H, H-2'), 4.02-4.11 (q, *J* 7.1 Hz, 2H, $CO_2CH_2CH_3$), 4.37 (br s, 1H, O*H*), 5.07 (d, *J* 9.5 Hz, H-4, major isomer) and 5.20 (m, H-4, minor isomer) (total 1H). ^{13}C NMR δ 13.8 (CH_3), 21.5 (CH_2), 24.7 (CH_2), 27.3 (CH_2), 30.6 (CH_2), 40.6 (CH_2), 55.9 (C-1), 60.8 (CH_2), 75.3 (C-6 or C-2'), 80.9 (C-2' or C-6), 81.0 (C-1'), 92.8 (C-4), 174.4 (*C*=O). These data are consistent with those described in the literature for the same compound.[6]

Ethyl (1*R,2*S**)-1-[2-(1,3-dioxolan-2-yl)ethyl]-2-acetoxy-2-ethynylcyclopentane-1-carboxylate (5a).** To a solution of alcohol **4a** (1.50 g, 5.30 mmol) and DMAP (0.200 g, 1.48 mmol) in Et_3N (2.2 mL) was added Ac_2O (1.14 mL, 11.9 mmol) and the mixture was stirred 2 h at r.t. After dilution with EtOAc (50 mL), H_2O/ice (aprox. 50 mL) was added. The layers were separated and the organic layer was washed successively with H_2O (50 mL), 1M HCl (50 mL) and NaOH 1M (50 mL), and dried (Na_2SO_4). The residue after evaporation was purified by flash chromatography (silica gel, 80:20 hexanes/EtOAc) to yield acetate **5a** (1.03 g, 60%): ^{1}H NMR δ 1.24 (t, *J* 7.1 Hz, 3H, C*H*$_3$), 1.54-1.86 (m, 6H), 2.06 (s, 3H, *C*H_3CO_2), 2.14-2.31 (m, 3H), 2.55-2.67 (m, 2H), 2.55 (s, H-2',

included en m at 2.55-2.67), 3.80-3.97 (m, 4H, OC*H*$_2$C*H*$_2$O), 4.14 (q, *J* 7.1 Hz, 2H, CO$_2$C*H*$_2$CH$_3$), 4.84 (apparent t, *J* 4.3 Hz, 1H, O-C*H*-O). ^{13}C NMR δ 14.0 (CH$_3$), 19.3 (CH$_2$), 21.6 (*C*H$_3$CO$_2$), 25.4 (CH$_2$), 29.6 (CH$_2$), 36.7 (CH$_2$), 60.7 (CH$_2$), 61.9 (C-1), 64.7 (CH$_2$), 75.0 (C-2'), 81.3 (C-1'), 81.7 (C-2), 104.2 (O-*C*H-O), 168.9 (*C*=O), 172.9 (*C*=O). IR (neat) υ 3270 (m, ≡C-H), 3000-2800 (m, C-H), 2110 (w, C≡C), 1750 (s, C=O), 1270 (m, C-O-C) cm^{-1}.

(1*R,2*S**)-Ethyl 2-acetoxy-2-ethynyl-1-(3-oxopropyl)cyclopentane-1-carboxylate (1a)**. A stirred solution of acetal **5a** (0.93 g, 2.87 mmol) in AcOH:H$_2$O (1/1.2, 2.1 mL) was refluxed for 1 h. After cooling to r. t., the solution was made neutral with sat. K$_2$CO$_3$ and extracted with EtOAc (4 x 30 mL). The combined organic layers were washed with brine (20 mL) and dried (Na$_2$SO$_4$). The residue after evaporation was purified by flash chromatography (silica gel, 80:20 hexanes/EtOAc) to yield aldehyde **1a** (0.68 g, 85%): ^{1}H NMR δ 1.25 (t, *J* 7.1 Hz, 3H, C*H*$_3$), 1.62-1.74 (m, 2H), 1.77-1.95 (m, 2H), 2.07 (s, 3H, *C*H$_3$CO$_2$), 2.23-2.58 (m, 5H), 2.59 (s, 1H, H-2'), 2.60-2.70 (m, 1H), 4.16 (q, *J* 7.1 Hz, 2H, CO$_2$C*H*$_2$CH$_3$), 9.77 (t, *J* 1.2 Hz, 1H, C*H*O). ^{13}C NMR δ 13.9 (CO$_2$CH$_2$*C*H$_3$), 19.6 (CH$_2$), 21.5 (*C*H$_3$CO$_2$), 23.4 (CH$_2$), 30.5 (CH$_2$), 36.8 (CH$_2$), 40.0 (CH$_2$), 60.9 (CH$_2$), 61.6 (C-1), 75.4 (C-2'), 80.9 (C-1'), 81.7 (C-2), 168.8 (O-*C*=O), 172.7 (O-*C*=O), 201.3 (H*C*=O). IR (neat) υ 3270 (m, ≡C-H), 3000-2800 (m, C-H), 2100 (w, C≡C), 1750 (s, C=O), 1730 (s, C=O) cm^{-1}. Anal. calcd for C$_{15}$H$_{20}$O$_5$: C, 64.26; H, 7.19. Found: C, 63.89; H, 7.32.

(1*R,2*R**)-Ethyl 1-[2-(1,3-dioxolan-2-yl)ethyl]-2-ethynyl-2-hydroxycyclohexane-1-carboxylate (4b)**. The procedure described above for the preparation of **4a** was followed starting from **3b**[28] (2.0 g, 7.4 mmol). The residue after evaporation was purified by flash chromatography (silica gel, 75:25 hexanes/EtOAc) to yield **4b** (2.1 g, 96%, 30:1 diast. mixture) as an oil: ^{1}H NMR δ 1.18-1.32 (m, 5H), 1.22 (t, *J* 7.1 Hz, CO$_2$CH$_2$*C*H$_3$, included in m at 1.18-1.32), 1.43-2.03 (m, 10H), 2.40 (s, 1H, C≡C-*H*), 3.73-3.90 (m, 4H, OC*H*$_2$C*H*$_2$O), 4.15 (qd, *J* 7.1, 2.6 Hz, 2H, CO$_2$C*H*$_2$CH$_3$), 4.40 (s, 1H, O*H*), 4.75 (m, 1H, O-C*H*-O). ^{13}C NMR δ 13.9 (CH$_3$), 19.6 (CH$_2$), 21.6 (CH$_2$), 22.4 (CH$_2$), 26.6 (CH$_2$), 28.5 (CH$_2$), 33.1 (CH$_2$), 53.0 (C-1), 60.7 (CH$_2$), 64.5 (CH$_2$), 71.4 (C-2 or C-2''), 72.9 (C-2'' or C-2), 85.5 (C-1''), 103.7 (O-*C*H-O), 176.3 (*C*=O). IR (neat) υ 3600-3400 (br, O-H), 3300-3200 (m, ≡C-H), 3000-2800 (m, C-H), 2100 (w, C≡C), 1740 (s, C=O), 1270 (m, C-O-C) cm^{-1}.

(1*R,8*R**)- Ethyl 6-ethynyl-4-hydroxy-5-oxabicyclo[4.4.0]decanecarboxylate (6b)**. The procedure described above for the preparation of **6a** was followed starting from **4b** (0.20 g, 0.67 mmol). The crude product was purified by flash chromatography (silica gel, 80:20 hexanes/EtOAc) to yield **6b** (0.14 g, 82%): ^{1}H NMR δ 1.22-1.95 (m, 12H), 1.25 (t, *J* 7.1 Hz, CO$_2$CH$_2$*C*H$_3$, included in m at 1.22-1.95), 2.03-2.31 (m, 2H), 2.43-2.56 (m, 2H), 2.53 (s, H-2', included in m at 2.43-2.56), 4.15 (q, *J* 7.1 Hz, 2H, CO$_2$C*H*$_2$CH$_3$), 4.37 (d, *J* 5.7 Hz, 1H, O*H*), 5.35 (ddd, *J* 9.7, 5.7, 3.0 Hz, 1H, H-4). ^{13}C NMR δ 14.0 (CH$_3$), 20.1 (CH$_2$), 21.7 (CH$_2$), 27.9 (CH$_2$), 28.2 (CH$_2$), 28.9 (CH$_2$), 35.8 (CH$_2$), 47.3 (C-1), 60.5 (CH$_2$), 73.0 (C-6 or C-2'), 75.0 (C-2' or C-6), 83.7 (C-1'), 93.3 (C-4), 173.7 (*C*=O). These data are consistent with those described in the literature for the same compound.[6]

(1*R,2*R**)-2-[2-(1,3-dioxolan-2-yl)ethyl]-2-(ethoxycarbonyl)-1-ethynylcyclohexyl benzoate (5b)**. The procedure described above for the preparation of **4a** was followed starting from **3b**[28] (1.00 g, 3.7 mmol). When the reaction mixture reached r. t., benzoyl chloride (0.47 mmol, 4.05 mmol) was added, the mixture was stirred at r. t. for 1 h and then at 50 °C for a further 1 h. After cooling to r. t., sat. NH$_4$Cl (30 mL) was added, the layers were separated, the aqueous layer was extracted with EtOAc (3 x 50 mL) and the combined organic layers were dried (Na$_2$SO$_4$). The residue after evaporation was purified by flash chromatography (silica gel, 80:20 hexanes/EtOAc) to yield benzoate **5b** (1.37 g, 92%): ^{1}H NMR δ 1.20 (t, *J* 7.1 Hz, 3H, CO$_2$CH$_2$*C*H$_3$), 1.26-1.74 (m, 6H), 1.83-2.18 (m, 4H), 2.41 (td , *J* 12.8, 4.4 Hz, 1H), 2.69-2.78 (m, 2H), 2.69 (s, H-2', included in m at 2.69-2.78), 3.78-3.98 (m, 4H, OC*H*$_2$C*H*$_2$O), 4.16 (q, *J* 7.1 Hz, 2H, CO$_2$C*H*$_2$CH$_3$), 4.88 (t, *J* 4.5 Hz, 1H, O-C*H*-O), 7.43 (apparent t, 2H, Ar-*H*), 7.54 (apparent t, 1H, Ar-*H*), 8.07 (d, *J* 7.7 Hz, 2H, Ar-*H*$_{ortho}$). ^{13}C NMR δ 14.2 (CH$_3$), 20.1 (CH$_2$), 22.0 (CH$_2$), 23.7 (CH$_2$), 27.9 (CH$_2$), 28.9 (CH$_2$), 31.5 (CH$_2$), 54.3 (C-2), 60.8 (CH$_2$), 64.9 (CH$_2$), 77.1 (C-2'), 78.3 (C-1), 80.8 (C-1'), 104.3 (O-*C*H-O), 128.3 (Ar-*C*H), 129.8 (Ar-*C*H), 130.9 (Ar-*C*), 132.9 (Ar-*C*H), 164.1

(*C*=O), 173.1 (*C*=O). IR (neat) υ 3260 (m, ≡C-H), 3000-2800 (m, C-H), 2113 (w, C≡C), 1725 (s, C=O), 1270 (m, C-O-C) cm^{-1}.

(1*R,2*R**)-2-(Ethoxycarbonyl)-1-ethynyl-2-(3-oxopropyl)cyclohexyl benzoate (1b)**. The procedure described above for the preparation of **1a** was followed starting from acetal **5b** (1.2 g, 3.0 mmol). The crude product was purified by flash chromatography (silica gel, 80:20 hexanes/EtOAc) to yield aldehyde **1b** (0.81 g, 76%) as a thick oil: ^{1}H NMR δ 1.22 (t, *J* 7.1 Hz, 3H, C*H*$_3$), 1.26-1.46 (m, 1H), 1.52-1.69 (m, 3H), 1.71-1.86 (m, 1H), 2.10-2.24 (m, 3H), 2.43-2.76 (m, 5H), 2.73 (s, H-2' included in m at 2.43-2.76), 4.19 (q, *J* 7.1 Hz, 2H, $CO_2CH_2CH_3$), 7.45 (apparent t, 2H, Ar-*H*), 7.54 (t, *J* 7.3 Hz, 1H, Ar-*H*), 8.06 (d, *J* 7.8 Hz, 2H, Ar-*H*$_{ortho}$), 9.81 (s, 1H, C*H*O). ^{13}C NMR δ 13.9 (CH_3), 20.1 (CH_2), 21.5 (CH_2), 22.0 (CH_2), 28.2 (CH_2), 31.4 (CH_2), 39.2 (CH_2), 53.8 (C-2), 60.9 (CH_2), 77.0 (C-2'), 77.8 (C-1), 80.6 (C-1'), 128.2 (Ar-*C*H), 129.5 (Ar-*C*H), 130.5 (Ar-*C*), 132.8 (Ar-*C*H), 163.8 (O-*C*=O), 172.5 (O-*C*=O), 200.9 (H*C*=O). IR (neat) υ 3263 (m, ≡C-H), 3000-2800 (m, C-H), 2113 (w, C≡C), 1722 (s, C=O) cm^{-1}. MS (EI) *m/z* (%) 356 (M), 299 (3), 177 (5), 105 (base), 77 (7). HRMS calcd for $C_{21}H_{24}O_5$ 356.1624, found 356.1611.

(1*S,2*R**)-2-[2-(1,3-dioxolan-2-yl)ethyl]-1-[4-(benzyloxy)but-1-yn-1-yl]-2-(ethoxycarbonyl)cyclopentyl benzoate (5c)**. To a solution of 4-benzyloxybut-1-yne[29] (1.90 g, 12.0 mmol) in THF (20 mL) at -78 °C under Ar, was added *n*-BuLi (1.6 M en hexanos, 6.9 mL, 11.0 mmol) and the solution was stirred for 30 min at the same temperature. A solution of ketone **3a** (2.50 g, 9.90 mmol) in THF (10 mL) was added, and the solution was allowed to reach r. t. Benzoyl chloride (11.0 mmol) was added and the mixture was stirred for 3h. Sat. NH_4Cl (20 mL) was added, the layers were separated, the aqueous layer was extracted with EtOAc (3 x 50 mL), and the combined organic layers were dried (Na_2SO_4). The residue after evaporation was purified by flash chromatography (silica gel, 80:20 hexanes/EtOAc) to yield benzoate **5c** (4.0 g, 80 %, a 31:1 diastereomeric mixture) as an oil. Data for the major isomer: ^{1}H NMR δ 1.23 (t, *J* 7.1 Hz, 3H, C*H*$_3$), 1.59-1.91 (m, 6H), 2.23-2.42 (m, 3H), 2.50 (t, *J* 7.3 Hz, 2H, H-3'), 2.53-2.87 (m, 1H), 3.53 (t, *J* 7.3 Hz, 2H, H-4'), 3.80-3.98 (m, 4H, OCH_2CH_2O), 4.49-4.91 (m, 2H, $CO_2CH_2CH_3$), 4.49 (s, 2H, PhCH_2O), 4.89 (apparent t, 1H, O-C*H*-O), 7.22-7.33 (m, 5H, Ar-*H*), 7.44 (apparent t, *J* 7.4 Hz, 2H, Ar-*H*), 7.55 (apparent t, *J* 7.3 Hz, 1H, Ar-*H*), 8.05 (d, *J* 7.7 Hz, 2H, Ar-*H*). ^{13}C NMR δ 14.1 (CH_3), 19.1 (CH_2), 20.1 (CH_2), 25.4 (CH_2), 29.0 (CH_2), 29.6 (CH_2), 36.7 (CH_2), 60.6 (CH_2), 62.3 (C-2), 64.8 (CH_2), 68.2 (CH_2), 72.8 (CH_2), 79.0 (C), 82.4 (C), 84.1 (C), 104.2 (O-*C*H-O), 127.4 (Ar-*C*H), 127.5 (Ar-*C*H), 128.2 (Ar-*C*H), 129.6 (Ar-*C*H), 129.8 (Ar-*C*), 130.8 (Ar-*C*), 132.8 (Ar-*C*H), 137.9 (Ar-*C*), 164.4 (*C*=O), 173.1 (*C*=O). IR (neat) υ 3000-2800 (s, C-H), 2247 (w, C≡C), 1725 (s, C=O), 1270 (m, C-O-C) cm^{-1}.

(1*S,2*R**)-1-[4-(Benzyloxy)but-1-yn-1-yl]-2-(ethoxycarbonyl)-2-(3-oxopropyl)cyclopentyl benzoate (1c)**. The procedure described above for the preparation of **1a** was followed starting from acetal **5c** (2.6 g, 5.2 mmol, 31:1 isomer mixture). The crude product was purified by flash chromatography (silica gel, 80:20 hexanes/EtOAc) to yield aldehyde **1c** (1.50 g, 63 %, 28:1 isomer mixture) as an oil. Data for the major isomer: ^{1}H NMR δ 1.24 (t, *J* 7.1 Hz, 3H, C*H*$_3$), 1.69-2.08 (m, 5H), 2.28-2.60 (m, 6H), 2.74-2.85 (m, 1H), 3.54 (t, *J* 7.3 Hz, 2H, H-4'), 4.15 (q, *J* 7.1 Hz, 2H, $CO_2CH_2CH_3$), 4.50 (s, 2H, PhCH_2O), 7.26-7.33 (m, 5H, Ar-*H*), 7.44 (t, *J* 7.1 Hz, 2H, Ar-*H*), 7.57 (apparent t, 1H, Ar-*H*), 8.05 (d, *J* 8.3 Hz, 2H, Ar-*H*), 9.78 (s, 1H, C*H*O). ^{13}C NMR δ 14.1 (CH_3), 19.5 (CH_2), 20.1 (CH_2), 23.7 (CH_2), 30.2 (CH_2), 37.0 (CH_2), 40.2 (CH_2), 60.9 (CH_2), 62.2 (C-2), 68.2 (CH_2), 72.9 (CH_2), 78.7 (C), 82.7 (C), 84.7 (C), 127.6 (Ar-*C*H), 128.3 (Ar-*C*H), 128.4 (Ar-*C*H), 129.6 (Ar-*C*H), 130.7 (Ar-*C*), 133.0 (Ar-*C*H), 137.9 (Ar-*C*), 164.4 (*C*=O), 172.9 (*C*=O), 201.4 (H*C*=O). IR (neat) υ 3000-2800 (m, C-H), 2248 (w, C≡C), 1725 (s, C=O) cm^{-1}. MS (EI) *m/z* (%) 476 (M), 325 (19), 105 (base), 91 (45), 84 (30). HRMS calcd for $C_{29}H_{32}O_6$ 476.2199, found 476.2196.

General Procedure for Et_2Zn/Pd(0)-mediated Cyclizations. In a typical experiment, to a solution of propargyl ester **1** (0.300 mmol) and $Pd(PPh_3)_4$ (0.015 mmol, 5 mol%) in benzene (3 mL) was added $ZnCl_2$ (where appropriate, see Table 1, (1.0 M in Et_2O, 0.360 mmol), followed by Et_2Zn (1.0 M in hexanes, 900 L, 0.90 mmol) at room temperature under Ar, and the reaction mixture was stirred for the time indicated in Table 1. After

diluting with EtOAc (10 mL), the solution was successively washed with 1 M HCl (5 mL), sat. $NaHCO_3$ (5 mL) and brine (5 mL), and dried (Na_2SO_4). The residue after evaporation was purified by flash chromatography (silica gel, 80:20 hexanes/EtOAc) to yield bicyclic products **2**. Characterization data for the individual compounds is given below.

***(1R*,4R*,5R*)*-Ethyl 5-ethynyl-4-hydroxybicyclo[3.3.0]octanecarboxylate (2a)**. Obtained from **1a**. The crude product was purified by flash chromatography (silica gel, 80:20 hexanes/EtOAc). ^{1}H NMR δ 1.26 (t, *J* 7.1 Hz, 3H, C*H*$_3$), 1.41-2.18 (m, 9H, that includes s at 2.18, H-2'), 2.27-2.52 (m, 3H), 4.12 (q, *J* 7.1 Hz, 2H, $CO_2CH_2CH_3$), 4.37 (m, 1H, H-4). ^{13}C NMR δ 14.1 (CH_3), 26.2 (CH_2), 31.5 (CH_2), 31.9 (CH_2), 35.2 (CH_2), 38.2 (CH_2), 56.4 (C), 60.7 (C), 63.9 (CH_2), 70.3 (C-2'), 80.1 (C-4), 88.5 (C-1'), 175.4 (*C*=O). These data are consistent with those described in the literature for the same compound.[4,6]

***(1R*,7R*)*-Ethyl 6-ethynyl-7-hydroxybicyclo[4.3.0]nonanecarboxylate (2b)**. Obtained from **1b**. The crude product was purified by flash chromatography (silica gel, 80:20 hexanes/EtOAc) and the isomers were separated by HPLC (65:35 hexanes/EtOAc, 8 mL/min), to yield **2b** and a minor diastereoisomer (**2b'**). Data for **2b**: t_R = 27 min. ^{1}H NMR δ 1.24 (t, *J* 7.1 Hz, 3H, C*H*$_3$), 1.30-2.16 (m, 13H, that includes a s at 2.16, H-2'), 2.23-2.36 (m, 1H), 4.11 (q, *J* 7.1 Hz, 2H, $CO_2CH_2CH_3$), 4.75 (apparent t, 1H, H-7). ^{13}C NMR δ 14.1 (CH_3), 21.0 (CH_2), 21.4 (CH_2), 27.0 (CH_2), 27.8 (CH_2), 28.5 (CH_2), 29.3 (CH_2), 46.5 (C), 55.3 (C), 60.6 (CH_2), 71.0 (C-2'), 79.8 (C-7), 86.8 (C-1'), 176.1 (*C*=O). IR (neat) υ 3500-3400 (br, O-H), 3301 (m, ≡C-H), 3000-2800 (m, C-H), 2106 (w, C≡C), 1714 (s, C=O) cm^{-1}. MS (EI) *m/z* (%) 236 (M), 179 (base), 151 (59), 91 (30). HRMS calcd for $C_{14}H_{20}O_3$ 236.1412, found 236.1409. Data for the minor isomer **2b'**: t_R = 15 min. ^{1}H NMR δ 0.97-1.15 (m, 1H), 1.23 (t, *J* 7.1 Hz, 3H, C*H*$_3$), 1.46-2.19 (m, 12H), 2.45 (s, 1H, H-2'), 4.10 (q, *J* 7.1 Hz, 2H, $CO_2CH_2CH_3$), 4.63-4.74 (m, 1H, H-7). ^{13}C NMR δ 14.1 (CH_3), 22.2 (CH_2), 22.9 (CH_2), 28.4 (CH_2), 30.8 (CH_2), 32.2 (CH_2), 32.6 (CH_2), 54.5 (C), 55.8 (C), 60.4 (CH_2), 74.7 (C-7), 76.9 (C-2'), 84.5 (C-1'), 174.9 (*C*=O). IR (neat) υ 3500-3400 (br, O-H), 3295 (m, ≡C-H), 3000-2800 (m, C-H), 2100 (w, C≡C), 1714 (s, C=O) cm^{-1}. MS (EI) *m/z* (%) 236 (M), 179 (97), 163 (40), 151 (base), 91 (38). HRMS calcd for $C_{14}H_{20}O_3$ 236.1412, found 236.1411.

***(1R*,4R*,5R*)*- Ethyl 5-(4-benzyloxybut-1-ynil)-4-hydroxybicyclo[3.3.0]octanecarboxylate (2c)**. Obtained from **1c**. The crude product was purified by flash chromatography (silica gel, 80:20 hexanes/EtOAc). ^{1}H NMR δ 1.22 (t, *J* 7.1 Hz, 3H, C*H*$_3$), 1.37-2.15 (m, 8H), 2.26-2.53 (m, 4H), 2.42 (t, *J* 7.1 Hz, H-3', included in m at 2.26-2.53), 2.69 (br s, 1H, O*H*), 3.48 (t, *J* 7.1 Hz, 2H, H-4'), 4.07 (quint, *J* 7.1 Hz, 2H, $CO_2CH_2CH_3$), 4.29 (dd, *J* 10.1, 6.1 Hz, 1H, H-4), 4.50 (s, 2H, PhC*H*$_2$O), 7.26-7.33 (m, 5H, Ar-*H*). ^{13}C NMR δ 14.1 (CH_3), 20.0 (CH_2), 26.1 (CH_2), 31.4 (CH_2), 31.9 (CH_2), 35.4 (CH_2), 38.2 (CH_2), 56.7 (C), 60.5 (CH_2), 63.7 (C), 68.6 (CH_2), 72.7 (CH_2), 78.6 (C-1' or C-2'), 80.2 (C-4), 85.4 (C-2' or C-1'), 127.6 (Ar-*C*H), 128.3 (Ar-*C*H), 137.9 (Ar-*C*), 175.5 (*C*=O). IR (neat) 3500-3400 (br, O-H), 3000-2800 (m, C-H), 1722 (s, C=O) cm^{-1}. MS (EI) *m/z* (%) 356 (M), 265 (21), 191 (33), 91 (base). HRMS calcd for $C_{22}H_{28}O_4$ 356.1988, found 356.1992.

(1*R,7*R**)-1-(Hydroxymethyl)-6-ethynylbicyclo[4.3.0]nonan-7-ol (7)**. A solution of ester **2b** (53.0 mg, 0.220 mmol) in Et_2O (4 mL) was added to a suspension of $LiAlH_4$ (36.0 mg, 1.32 mmol) in Et_2O (6 mL) at 0 °C under Ar. The reaction mixture was allowed to reach r.t., and stirred for 4 days. After addition of EtOAc (4 mL), the mixture was filtered and the solid residue was washed with EtOAc (20 mL). The combined solution and washings was evaporated and the crude product was purified by was purified by flash chromatography (silica gel, 60:40 hexanes/EtOAc) to yield diol **7** (18 mg, 42%). The characterized sample was obtained after HPLC (10 mL/min, 50:50 hexanes/EtOAc). t_R = 44 min. ^{1}H NMR δ 1.33-1.93 (m, 13H), 2.04-2.24 (m, 1H), 2.27 (s, 1H, H-2'), 3.41 (d, *J* 11.3 Hz, 1H, C*H*OH), 3.64 (d, *J* 11.3 Hz, 1H, C*H*OH), 4.58 (t, *J* 8.6 Hz, 1H, H-7). ^{13}C NMR δ 21.2 (CH_2), 21.8 (CH_2), 26.0 (CH_2), 28.1 (CH_2), 28.4 (CH_2), 28.7 (CH_2), 46.2 (C), 47.9 (C), 70.5 (*C*H$_2$O), 72.1 (C-2'), 80.1 (C-7), 87.9 (C-1'). IR (neat) υ 3600-3400 (br, O-H), 3300 (s, ≡C-H), 3000-2800 (m, C-H), 2100 (w, C≡C) cm^{-1}. MS (EI) *m/z* (%) 194 (M), 137 (base), 91 (24), 79 (17). HRMS calcd for $C_{12}H_{18}O_2$ 194.1307, found 194.1302.

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Supplementary Material

Copies of ^{1}H and ^{13}C NMR spectra of new compounds.

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